(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 20 March 2003 (20.03.2003)

PCT

(10) International Publication Number WO 03/022251 A1

(51) International Patent Classification7: 9/16, C07C 229/00

A61K 9/14,

Srinivasan [IN/IN]; Alembic Limited, Alembic Road,

(21) International Application Number:

PCT/IB01/02080

(22) International Filing Date:

5 November 2001 (05.11.2001)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

871/MUM/2001

12 September 2001 (12.09.2001) IN

872/MUM/2001

12 September 2001 (12.09.2001)

(71) Applicant (for all designated States except US): ALEM-BIC LIMITED [IN/IN]; Alembic Road, Vadodara 390 003, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SHAH, Vrajesh [IN/IN]; Alembic Limited, Alembic Road, Vadodara 390 003, Gujarat (IN). HITKARI, Anurag [IN/IN]; Alembic Limited, Alembic Road, Vadodara 390 003, Gujarat (IN). DEO, Keshav [IN/IN]; Alembic Limited, Alembic Road. Vadodara 390 003, Gujarat (IN). RENGARAJU, Vadodara 390 003, Gujarat (IN).

- (74) Common Representative: DO, Keshav Alembic Limited; Alembic Road, Vadodara 390 003, Gujarat (IN).
- (81) Designated States (national): AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, ES, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,

Declaration under Rule 4.17:

of inventorship (Rule 4.17(iv)) for US only

Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NINE AND PROCESS OF PREPARATION

(54) Title: NOVEL STABLE CRYSTAL FORM OF N-TRANS-4-ISOPROPYLCYCLOHEXYL CARBONYL)-D-PHENYLALA-

(57) Abstract: This invention relates to novel stable crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine may be produced by crystallisation of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine with a solvent at 25 - 38 °C and forming crystals in the solvent. The crystal form may be formed by recrystallisation out of solution. The Crystal form obtained in this way have different melting point, infra red spectrum and X-ray diffraction patterns from previously known forms "B-type" and "H-Type" of the compound.

1

FORM 2

THE PATENTS ACT, 1970 (39 of 1970)

COMPLETE SPECIFICATION

- 1. NOVEL STABLE CRYSTAL FORM OF N- (TRANS-4-ISOPROPYLCYCLOHEXYL CARBONYL)-D-PHENYLALANINE AND PROCESS OF PREPARATION.
- M/S. ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA 390 003, GUJARAT, India, an Indian Company incorporated under the Companies Act, 1956.
- 3. The following specification describes and ascertains the nature of the invention and the manner in which it is to be performed.

FIELD OF THE INVENTION -

The present invention relates to novel stable crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine. The Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine have different melting point, infra red spectrum and X-ray diffraction patterns from previously known forms, "B-Type" and "H-Type" of the compound.

BACKGROUND OF THE INVENTION

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is disclosed in Japanese Patent Application Laid Open No. 63-54321 (equivalent to EP-A-196222 and US 4,816,484) and in J. Med. Chem. 32, 1436-41 (1989). "The Japanese application describes how the compound may be crystallized from aqueous methanol to yield crystals having a melting point of 129° to 130° C. These crystals are in a crystalline form referred to herein as "B-type". An infra red absorption spectrum and powder X-ray diffraction pattern are disclosed in the US patent no. 5463116 Oct. 31 1995".

The U.S. Pat no. 5463116 also describes how the compound may be crystallized from aqueous acetone, ethanol and isopropanol to yield different type of crystals having a melting point of 136⁰ to 142⁰ C. These crystals are in a crystalline form referred to herein as "H-type"."

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine of formula (1) is a known substance having therapeutic utility in depressing blood glucose levels.

(1)

The present inventors have made a novel stable crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

The crystals as formed by the present invention hereinafter designated as the "AL-type" crystals of N-(trans-4- isopropylcyclohexyl carbonyl)-D-phenylalanine are substantially stable to the physical grinding. Such crystals are therefore more suitable for use in medicines than the existing crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine

It is an objective of the present invention to provide a novel stable crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

It is a further objective of the present invention to provide a novel method for manufacturing the a stable crystalline new form of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine.

The new form is different than previously known disclosed forms: so called "B-type" and "H-type". The inventors have designated the new stable crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine as "AL-type".

REFERENCES-

1. US Patent 5463116.

Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D- phenylalanine and methods for preparing them.

Sumikawa M, Koguchi K, Ohgane T, Irie Y and Takahashi S.

Ajinomoto Co., Inc., Tokyo, Japan.

2. US Patent 4,816,484.

Hypoglycemic agent.

Toyoshima S, Seto Y, Shinkai H, Toi K and Kumashiro I.

Ajinomoto Co., Inc., Tokyo, Japan.

3. Shinkai H, Nishikawa M, Sato Y, Toi K, Kumashiro I, Seto Y, Fukuma M, Dan K, Toyoshima S.

N-(cyclohexylcarbonyl)-D-phenylalanines and related compounds. A new-class of oral hypoglycemic agents. 2.

J Med Chem. 1989 Jul;32 (7):1436-41.

DETAILED DESCRIPTION OF THE INVENTION-

The "AL-type" Crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine may be formed by crystallization from solution, the crystallization from solution taking place at a temperature between 30°C and the boiling point of the solvent.

The crystals thus formed generally comprise enhanced amounts of "AL-type" crystals relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

The crystallization at about 30 °C may be performed in several ways as will be apparent to those of skill in the art.-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine "B-type" crystals may be dissolved in a solvent in which it is readily soluble at higher temperature but in which it is only sparingly soluble at lower temperatures.

Solvents which are suitable for use in this invention may be selected from the group comprising dimethyl formamide, dimethylacetamide and acetonitrile.

More preferably the solvent is acetonitrile.

The dissolution volume of the solvent is preferably from 8 to 60 vol % of the solvent.

The temperature of the solution is preferably 55°C to 75°C.

The new crystals were obtained from the solution by filtration or centrifuging and then dried at a temperature in the range 50°C to 90°C

BRIEF DESCRIPTION OF THE ANNEXURES INCLUDING DRAWINGS

FIGURE 1. Shows differential scanning calorimeter (DSC) of "AL-type" crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

FIGURE. 2 :: Shows a powder X-ray diffraction pattern of "AL-type" crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in accordance with the present invention.

FIGURE. 3 :: Shows an infra red absorption spectrum of "AL-type" crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in accordance with the present invention.

FIGURE 4 :: Shows a crystals photograph of "AL-type" form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in accordance with the present invention.

FIGURE. 5 :: Shows a crystals photograph of "H-type" form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

FIGURE 6 :: Shows a crystals photograph of "B-type" form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a stable "AL- type" crystalline form of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine. The various examples of the physical properties of the "AL-type" crystal form of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine are as follows.

The inventors have measured the melting point of new "AL-type" crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine and found it to be in the range of 174° to 178° C.

Similarly, when the melting points of both the previously known "B-type" & "H-type" crystals were taken by same technique, melting points were found 127^{0} to 130^{0} C and 136^{0} to 140^{0} C. respectively.

The powder X-ray diffraction patterns of new "AL-type" crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine as shown in Anex-2 is obtained by using a Philips PW1700 powder diffractometer and a scan speed of 0.05.degree./sec. The observed powder X-ray diffraction patterns of new "AL-type" crystals is different than the disclosed X-ray diffraction patterns in patent

US 5463116 for "B-type" & "H-type" crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine.

The inventors carried out the CHN analysis of all three "B-type" ,"H-type" and "AL-type" crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine and the results are shown as below.

Nolecular Formula :: C ₁₉ H ₂₇ N O ₃			
	C %	H %	N %
heoretical Value	71.89	8.57	4.41
bserved Value for "AL-type"	71.75	8.76	4.09
bserved Value for "H-type"	71.92	8.44	4.41
bserved Value for "B-type"	71.92	8.96	4.17

These results confirm that the all three "B-type", "H-type"and new "AL-type"crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine have the similar composition.

The new "AL-type" crystals of N-(trans-4- isopropylcyclohexyl carbonyl)-D-phenylalanine are preferably substantially stable to the physical grinding. Stability to grinding may be assessed by measurement of physical property before and after grinding. Where the physical property remains substantially unchanged. Suitable physical properties for measurement includes melting point, differential scanning calorimeter and infra red absorption spectrum.

The photographs as shown in Anex - 4 - 6 of all three "AL-type", "H-type" and "B-type", crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine were taken by using a Phillips XL-30 electron microscope. The crystal shape of new "AL-type" crystals is substantially different than the other known both "B-type" & "H-type" crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine.

The "AL-type" Crystals of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine may be formed by crystallization from solution, the crystallization from solution taking place at a temperature between 30°C and the boiling point of the solvent. The crystals thus formed generally comprise enhanced amounts of "AL-type" crystals relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

The crystallization at about 30 °C may be performed in several ways as will be apparent to those of skill in the art.-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine "B-type" crystals may be dissolved in a solvent in which it is readily soluble at higher temperature but in which it is only sparingly soluble at lower temperatures. Solvents which are suitable for use in this invention include dimethyl formamide, dimethylacetamide and acetonitrile. A preferred solvent is acetonitrile. The dissolution volume of the solvent is preferably from 8 to 60 vol % of the solvent. The temperature of the solution is preferably 55° C to 75°C. The new crystals were obtained from the solution by filtration or centrifuging and then dried at a temperature in the range 50°C to 90°C.

The invention will now be more concretely illustrated by the following examples but the invention may note be construed to be limited thereto.

EXAMPLES

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for use in the following examples was obtained by the method described in Example 3 of Japanese patent application laid open no. 63-54321. The product consists crystals of "B-type".

Example-1

A solution of 10 g of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine "B-type" in 120 ml of an acetonitrile is stirred at 55 – 60° C. After cooling to 30 - 35° C., the precipitated crystals were filtered and dried at 70-80° C. at reduced pressure overnight. 3.5 g of dry crystals were obtained. The crystals had a melting point of 174° to 178° C. The powder X-ray diffraction pattern and the infra-red absorption spectrum were measured and the crystals were identified as "AL-type", and the required analytical tests are carried { NMR, I.R., XRD, DSC, as depicted in the annexures }, by which it can be concluded that the novel crystal formed are stable. The formed crystale are "AL-type". "AL-type"

Example- 2

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine "B-type" (5 g) was dissolved in acetonitrile 60 ml. at 55 - 60° C. The solution was cooled with stirring. "AL-type" crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (0.1 g) prepared in Example 1 were added at a temperature of 30 - 38° C and the solution was cooled further to 25° C. The crystals were filtered and dried at 70-80° C. overnight and at reduced pressure. 1.5 g of dry crystals were obtained. The crystals had a melting-point of 174° to 178° C. The powder X-ray diffraction pattern and the infra-red absorption spectrum enabled the crystals to be identified as "AL-type"

We claim-

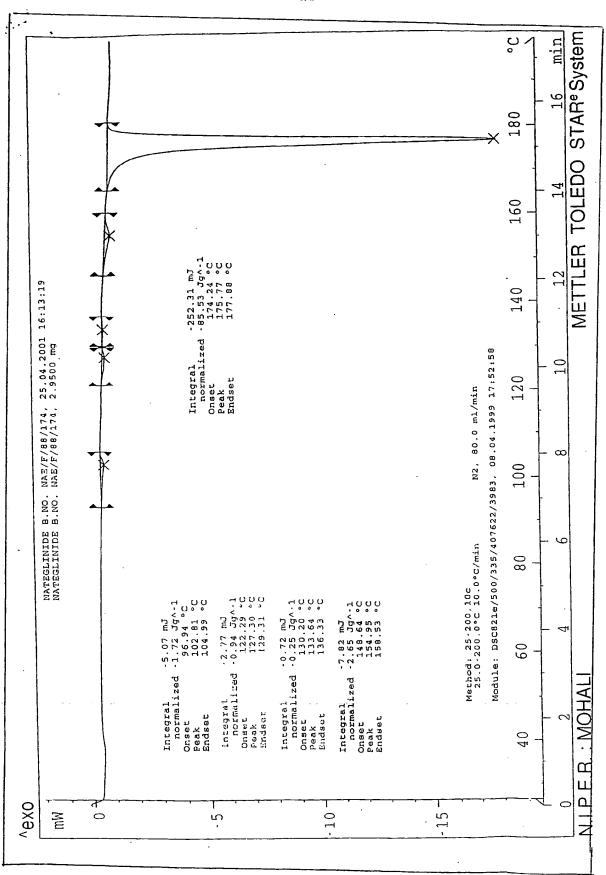
- An isolated novel stable crystal form of N-(trans-4-isopropylcyclo hexyl carbonyl)-D-phenylalanine having the following physical properties:
 - (a) A melting point in the range of 174°-178°C. Anex.-1.
 - (b) A powder X-ray diffraction pattern with reflection maxima at 2.theta. of
 - about 7.5.0., 15.5.0., 19.8.0. and 20.2.0.; Anex.-2.
 - (c) An infra red absorption spectrum with critical absorption bands in the region of 1711.5, 1646.5, 1538.7,1238.8 ,1215.1 and 700.5 cm. Anex.-3.
- 2. An isolated novel stable crystal form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine having an X-ray powder diffraction pattern as shown in Anex.-2.and an infra red spectrum as shown in Anex.-3.
- 3. Novel stable crystal form of N-(trans-4-isopropylcyclohexyl carbonyl)-D-phenylalanine according to any one of claims 1 and 2 being substantially free of solvent.
- 4. A process for preparing the novel stable crystal form of N-(trans-4-isopropylcyclo hexylcarbonyl)-D-phenylalanine which comprises dissolving N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in a solvent in which it is soluble at a temperature greater than 60°C to form a solution, crystallizing the said solution by cooling to a temperature of 28°C or higher, and obtaining the desired crystals at a temperature in excess of 28°C.

- 5. A process as claimed in claim 4 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is dissolved in the solvent at a temperature between 60°C to 75°C.
- 6. A process as claimed in claim 4 wherein the precipitation of the solution is carried out at a temperature between 28° C to 35° C.
- 7. The process as claimed in claim 4 wherein the said crystals are separated from the solvent at a temperature of 38° C.
- 8. The process as claimed in claims 4 and 5 wherein the solvent is a water miscible polar solvents, selected from the group comprising acetonitrile, dimethyl formamide and dimethyl acetamide.
- 9. The process as claimed in claim 4 and 8 wherein the water miscible polar solvent is acetonitrile.
- 10. The process as claimed in claim 4 wherein the concentration of the said solvent is from 8 to 20 vol % of the product.
- 11. An isolated novel stable crystal form of N-(trans-4-isopropylcyclo hexyl carbonyl)-D-phenylalanine substantially as herein described with reference to the foregoing description and the accompanying examples.

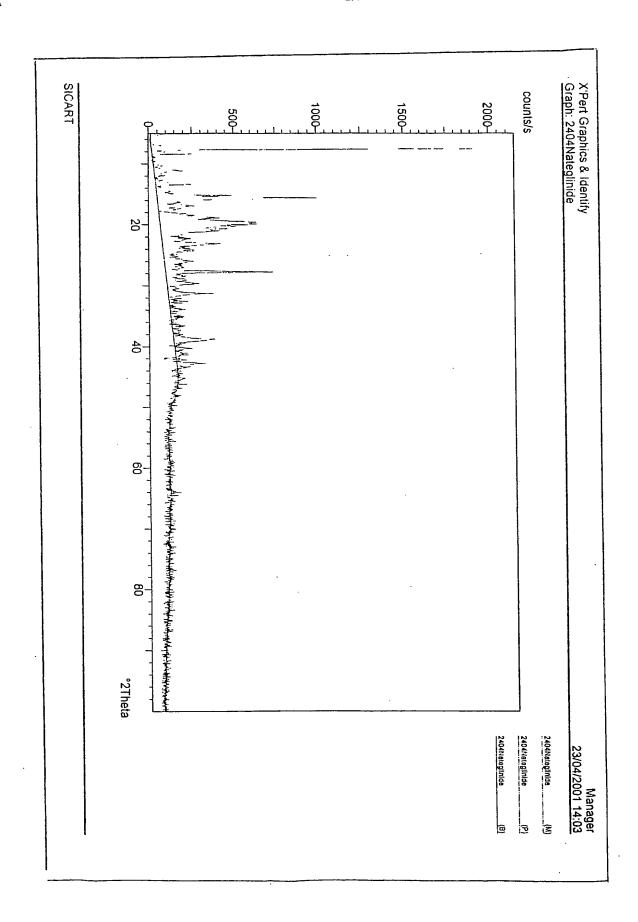
WO 03/022251 PCT/IB01/02080

14

12.A process for preparing the novel stable crystal form of N-(trans-4-isopropylcyclo hexylcarbonyl)-D-phenylalanine substantially as herein described with reference to the foregoing description and the accompanying examples.



2/8



X'Pert Graphics & Identify (searched) peak list: 2404Nateglinide

Manager 23/04/2001 14:03

Description:

NAteglinide B.No. NAE/F/88/174, Sample from Alembic Limited

Original scan: 2404Nateglinide

Date: 23/04/2001 12:25

Description of scan:

NAteglinide B.No. NAE/F/88/174, Sam

Used wavelength:

K-Alphal

K-Alpha1 wavelength (Å):

1.54056

K-Alpha2 wavelength (Å):

1.54439

K-Alpha2/K-Alpha1 intensity ratio:

0.50000

K-Alpha wavelength (Å):

1.54056

K-Beta wavelength (Å):

1.39222

Peak search parameter set:

Intensities

Set created:

27/04/2000 11:10

Peak positions defined by:

Minimum of 2nd derivative

Minimum peak tip width (°2Theta): Minimum peak tip width (°2Theta):

0.10

Peak base width (°2Theta):

1.00

2.00

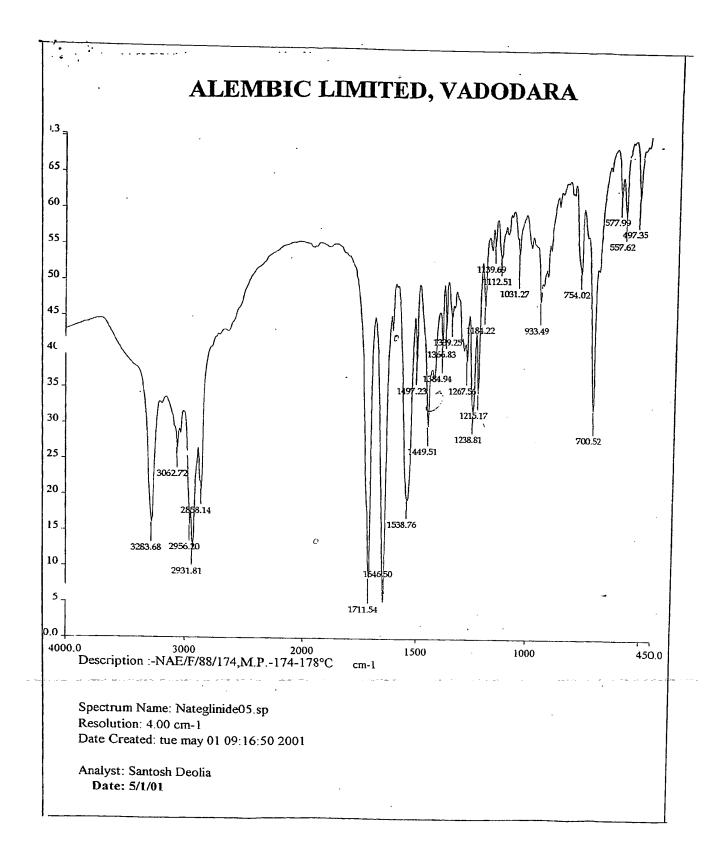
Minimum significance:

1.00

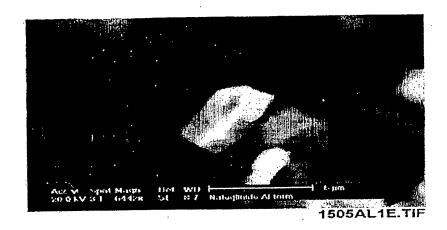
d-spacing	Relative Intensity	Angle	Peak	Background	Tip	Significance
(Å)	(%)	/90m	Height		Width	8
	(/0)	(°2Theta)	(counts/s)	(counts/s)	. (°2Theta)	
16.82425	2.70	5.24828	. 50.00			
11.65581	100.00	7.57836	52.29	11.08	0.48000	1.65
10.56445	11.91	8.36258	1936.33	17.27	0.24000	23.46
8.58238	3.05	10.29860	230.60	20.40	0.15000	2.33
7.96033	9.88	11.10581	59.10	28.13	0.24000	1.21
7.40534	3.05	11.70387	191.25	31.35	0.15000	1.16
6.62736	10.16	13.34884	59.08	34.68	0.18000	1.15
6.17499	4.71	14.33170	196.75	40.29	0.15000	1.20
5.84524	22.33	15.14481	91.19	44.22	0.24000	1.06
5.68507	51.70	15.57411	432.43	47.46	0.15000	2.26
5.25406	13.00		1001.16	49.17	0.21000	7.21
5.08340	6.05	16.86064	251.77	54.30	0.21000	1.66
4.90743	6.83	17.43103	117.07	56.58	0.24000	1.38
4.72093	16.42	18.06119	132.17	59.09	0.18000	1.03
4.55838	26.58	18.78104	317.88	61.97	0.24000	1.48
4.46259		19.45715	514.72	64.66	0.36000	2.41
4.37492		19.87900	560.46	66.35	0.18000	1.09
4.21705	21.99	20.28153	425.75	67.95	0.18000	1.46
3.98643	16.14	21.04930	312.50	71.02	0.18000	1.18
3.70043	7.50	22.28214	145.21	75.93	0.42000	1.77
ICART						
						Page: 1

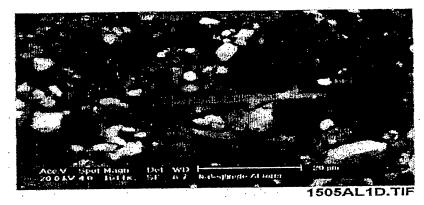
•	3.7
Trem . O. 11:- 9- Idontify	Manager
X'Pert Graphics & Identify	22 /04 /2004 44.02
(searched) peak list: 2404Nateglinide	23/04/2001 14:03
(searched) peak list 240414ateguitee	

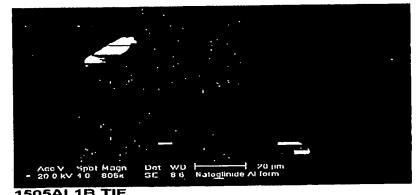
d-spacing	Relative	Angle	Peak Height	Background	Tip Width	Significance
(Å)	Intensity (%)	(°2Theta)	(counts/s)	(counts/s)	(°2Theta)	
3.84376	18.60	23.12044	360.07	79.28	0.15000	1.12
3.67223	6.88	24.21635	133.19	83.65	0.48000	1.33
3.43752	7.24	25.89759	140.22	90.36	0.48000	1.59
3.21926	32.77	27.68722	634.60	97.50	0.21000	6.08
3.07128	5.79	29.04983	112.08	102.93	0.30000	1.14
3.01006	8.67	29.65411	167.85	105.35	0.36000	2.62
2.85663	10.51	31.28645	203.58	111.86	0.21000	1.81
2.64343	3.56	33.88285	68.89	122.22	0.36000	2.01
2.55979	2.47	35.02520	47.90	126.77	0.48000	1.99
2.43876	1.84	36.82421	35.62	133.95	0.72000	1.32
2.32028	11.58	38.77772	224.32	141.74	0.42000	3.79
2.23644	4.69	40.29315	90.80	147.79	0.24000	1.04
2.11748	7.69	42.66401	149.00	157.25	0.30000	2.41

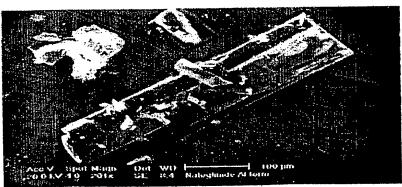


6/8

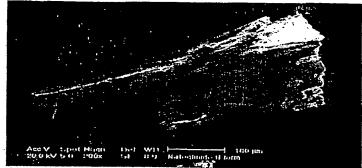




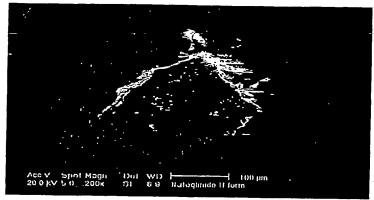




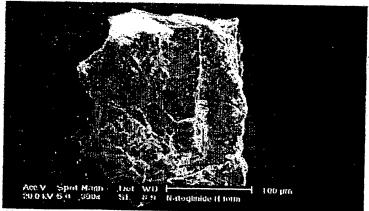
1505AL1A.TIF



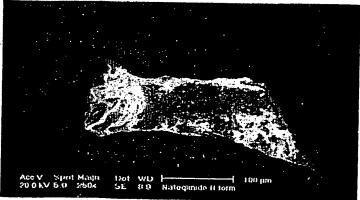
1505AL2A.TIF



1505AL2B.TIF

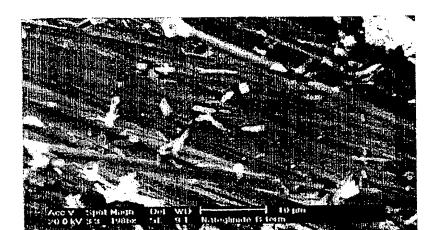


1505AL2C-TIF



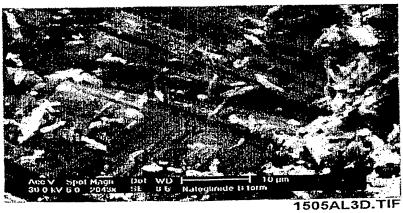
1505AL2D.TIF

BEST AVAILABLE COPM 1/02080









INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB01/02080

A. CLA	SCIEICATION OF CUIP TO CONTACT		PC1/18	£01702080		
IPC(7)	SSIFICATION OF SUBJECT MATTER					
US CL	: A61K 9/14, 9/16; C07C 229/00 : 424/489, 490; 562/450, 4344					
According to	o International Patent Classification (IPC) or to bo					
B. FIEL	DS SEARCHED	th national classification a	nd IPC			
U.S. 4	ocumentation searched (classification system follow 24/489, 490; 562/450, 4344	ved by classification symb	ols)			
0.5. 4	241409, 490; 302/430, 4344					
 						
Documentation	on searched other than minimum documentation to	the outent that 1				
į	and a second to the second to	the extent that such docar	ments are include	d in the fields searched		
ł	•					
			·			
Electronic da	ta base consulted during the international search (name of data have and wh	ara menetia. Li			
EAST	,	and of data oast and, wil	cie practicable, s	earch terms used)		
C. DOCI	JMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of desired 10 BE RELEVANT					
Y	Citation of document, with indication, where	appropriate, of the releva	nt passages	Relevant to claim No.		
1	US 5,463,116 A (SUMIKAWA et al.) 31 Octobelines 20-65.	wr 1995 (31.10.1995), see	column 10.	1-8, 10-12		
	Imes 20-05.		,	1 0, 10 12		
-						
			1			
				1		
			1	1		
1			I	1		
j			Ì	ļ		
				1		
ļ			[ļ		
				ł		
1						
			1			
			1			
}						
		•		1		
				1		
Further d	locuments are listed in the continuation of Box C.					
	cial categories of cited documents:	See patent fan				
		"T" later document pu	blished after the interr	ational filing date or priority		
"A" document de of particular	fining the general state of the art which is not considered to be		nflict with the applicat y underlying the invent			
				Į.		
"E" carlier applie	cation or patent published on or after the international filing date	considered novel	cular relevance; the cl	aimed invention cannot be d to involve an inventive step		
'L" document wh	hich may throw doubts on priority claim(s) or which is cited to	when the documen	nt is taken alone	- w manage are inventive steb		
establish the specified)	publication date of another citation or other special reason (as	"Y" document of parti-	cular relevence 4 .			
apcuncuy	•	considered to invo	live an inventive gien u	aimed invention cannot be		
O" document ref	ferring to an oral disclosure, use, exhibition or other means	- Committee with on	t of more other such d	Ocumente such combined		
	blished prior to the international filing date but later than the	ceing obvious to a	person skilled in the s	rt (
priority date	claimed	"&" document member	of the same patent far	nily		
Date of the actu	al completion of the international search			_		
		Date of mailing of the	ternational search	himport		
1 June 2002 (0	1 June 2002 (01.06,2002)					
Vame and maili	ng address of the ISA/US	Authorize lofficer				
Commiss Box PC	sioner of Patents and Trademarks	TOTAL !	< NUADINO			
Washing	ton, D.C. 20231	Amy E Pulliam		Λ		
acsimile No. (acsimile No. (703)305 3030					
Telephone No. 703-308-0196 m PCT/ISA/210 (second sheet) (July 1998)						
	·····					

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB01/02080

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)						
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:						
1.		Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:				
2.		Claim Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:				
3.	6.4(a).	Claim Nos.: 9 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule				
Box	II Ob	servations where unity of invention is lacking (Continuation of Item 2 of first sheet)				
This	Internat	ional Searching Authority found multiple inventions in this international application, as follows:				
1.		As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.				
2.		As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.				
3.		As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:				
4.		No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:				
Ren	nark on	Protest				

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

THIS PAGE BLANK (USPTO)